TO: Division of Dockets Management [HFA-305]
Food and Drug Administration
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FROM: Karl M. Nelson, Ph.D. KMN
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DATE: March 22, 2005

RE: Docket No. 2005N-0038
Reporting of Adverse Events to IRBs

1. The Role Of IRBs In The Review Of Adverse Events Information From Ongoing Clinical Trials

   IRBs play an important role in the protection of human subjects involved in research. As IRBs (and investigators) review adverse event information from an ongoing trial, they are asked to make two decisions:

   (a) Does this adverse event require a change in the consent form; and
   (b) Does this adverse event require a change in the research protocol?

   With respect to these decisions, it is immaterial whether the adverse event information is from an ongoing multi-site trial or a single-site trial.

2. The Types Of Adverse Events About Which IRBs Should Receive Information

   IRBs need to be informed about all adverse events. This is because IRBs need to be able to see how their site compares with other sites. Their adverse event history may be similar to other sites or may differ significantly from other sites. For example, Site A enrolls four subjects in a trial and they all die. This may indicate a significant problem with the investigational agent or it may indicate a systemic problem with the medical care provided at the site.

3. Approaches To Providing Adverse Events Information To IRBs

   This is the crux of the issue. How should adverse event information be provided to IRBs and Investigators? Can they receive the information in a format that permits them to make decisions about changes to consent forms and/or the protocol?

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Adverse events are not created equal. They can be:

(a) Serious or not-serious;
(b) Expected or unexpected; and
(c) Have an attribution of unrelated, or unlikely, possibly, probably, or definitely related to the test article.

IRBs should receive detailed information about each adverse event that is serious, unexpected and with an attribution of possibly, probably or definitely related to the test article in a timely fashion. This will permit them to make a decision about changes in the consent form and/or protocol. However, if an unexpected, serious adverse event occurs several times, then it is no longer unexpected and should be included in the consent form. When that happens, the IRB and Investigator need not be informed of each separate occurrence. It can then be provided in a summary form.

All other adverse event information should be provided in summary form at appropriate intervals. The adverse event information provided in ECOG Progress Reports is very useful. IRBs and Investigators are provided with the number (or percent) of occurrences of adverse events; the grade or severity; and the experimental group in which it occurred.

At the time of initial review, risks are classified as:

(a) Likely [>20%]
(b) Less Likely [5-20%]
(c) Rare but serious [<5%]

IRBs should receive information that permits them to asses the incidence of adverse events. The ECOG Progress Reports let the IRB and Investigator determine if an adverse event is occurring more frequently than anticipated.